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Heart rate variability and myocardial infarction: systematic literature review and metanalysis

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Abstract. – *Background:* **Heart rate, measured as beat-to-beat intervals, is not constant and varies in time. This property is known as heart rate variability (HRV) and it has been investigated in several diseases, including myocardial infarction (MI). The main hypothesis is that HRV embed some physiological processes that are characteristics of regulatory systems acting on cardiovascular system. It is possible to quantify such a complex behaviour starting from RR intervals properties itself with the idea that any event affecting the cardiac regulatory system significantly will disrupt and change HRV. In this article, we first review different methodologies previously published to calculate HRV indexes. We then searched literature for studies published on HRV and MI and we derive a metanalysis where published data allow calculation of composite outcomes.**

Material and Methods: **Articles considered eligible for metanalysis were original retrospective/prospective studies investigating HRV after myocardial infarction, reporting follow up for mortality or significant cardiac complications. Random effect model was used to assessed for homogeneity and calculate composite outcome and its 95% confidence interval (CI).**

Results: **21 studies were identified as eligible for subsequent analysis. Among these studies 5 large trials were eligible for metanalysis: "they included 3489 total post-MI patient with an overall mortality of 125/577 (21,7%) in patients with standard deviation of RR intervals (SDNN) less than 70 msec compared to 235/2912 (8,1%) in patients with SDNN >70 msec". Metanalysis demonstrates that, after a MI, patients with SDNN below 70 msec on 24 hours ECG recording have almost 4 times more chance to die in the next 3 years.**

Conclusion: **Results from metanalysis and other studies considered (but not included in the analysis) are consistent with the final finding, that a disrupted HRV dynamic (low SDNN) is associated with higher adverse outcome. In this perspective, although data are strongly positive for a direct relationship between SDNN and mortality after MI, SDNN value must be considered carefully on a single patient. The primary purpose of the metanalysis was to address whether studies conducted on HRV and MI were consistent rather than established a cut-off for SDNN. HRV is simple, non invasive and relatively not expensive to obtain.**

Key Words:

Heart rate variability, Myocardial infarction, Metanalysis, Coronary artery disease, Sympathovagal balance, Fractal.

Introduction

Almost fifty years ago, Schneider and Costiloe[1] reported that, in human beings, heart rate, measured as beat-to-beat intervals, is not constant and varies in time. This observation led to a field of studies that investigated heart rate variability (HRV) in several diseases, including coronary artery disease and myocardial infarction (MI).

HRV can simply be obtained using one lead chest ECG trace from which R to R intervals are measured in milliseconds and plotted in sequence. Thus, HRV is a measure of electrical activity and not mechanical activity as the name might suggest.

Plotting RR intervals visually helps to better understand some features. Figure 1 illustrates recording from a healthy subject in awake, supine, resting position.

Panel A shows a randomly selected 1000 consecutive RR intervals. Clearly, fluctuations are seen on small time scales (respiration) and also on long time scales. Panels B through D show respectively mean, standard deviation (SD) and Kurtosis of local trends, based on 500 RR samples centered for the respective RR interval. In

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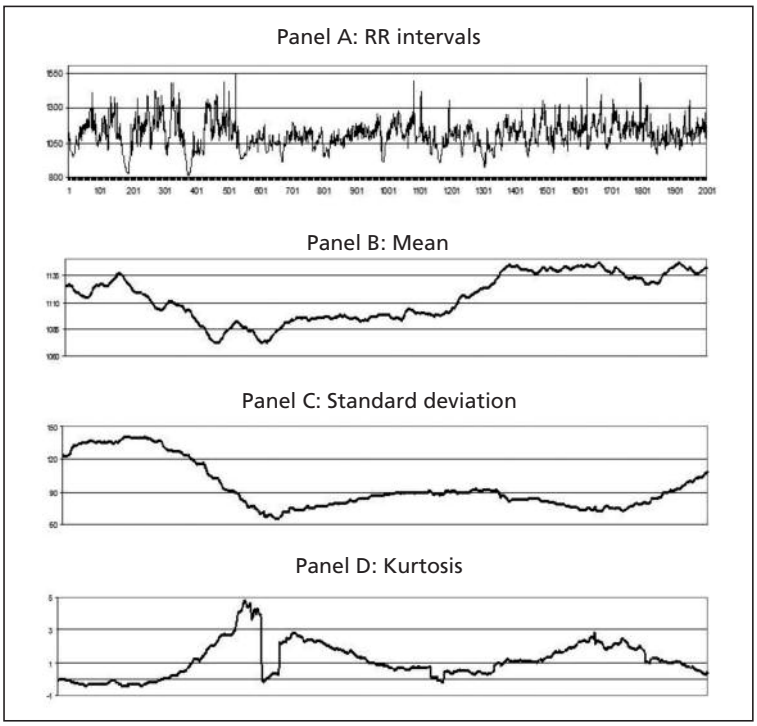

Figure 1. Panel A: RR intervals from a 51 year old male patient with normal cardiac angiography and in no medications at home. Panel B, C and D: for each RR interval on panel A, mean, standard deviation and Kurtosis are obtained considering 250 RR before and after (500 RR total).

other words, for the *nth* RR interval on panel A, panels B through D show the specified parameter based on 250 RR intervals before and after.

As easily noted, local means are not stationary, i.e. they do not stay stable over time. Standard deviation and Kurtosis are inversely correlated as expected. What is notable is their range of variation. For SD, the percent variation is up to 50% and Kurtosis ranges from around 0 up to 4.

In particular, Kurtosis is a mathematical tool used to check for normal distribution in a set of data. It is an index of "how peaked" is the distribution around its mean. Commonly, a distribution is considered "normal" (i.e. Gaussian) when Kurtosis is between –1 and +1. As Figure 1 shows, heart rate shows local trends of non-normal distribution, characterized by high fluctuations periods (low Kurtosis and high SD) and low fluctuations periods (high Kurtosis and low SD). Local means' trend shows a direct relationship with SD and inverse relationship with Kurtosis. When local mean tends to decrease (mean heart rate increases), SD decreases as well, and Kurtosis increases indicating more variations around the mean value, and low extreme variations (also indicated by a low SD).

In a purely statistical aspect, Figure 1 shows that RR intervals must be, in some degree, correlated and their variation does not follow a random (Gaussian) distribution. In other words, one can demonstrate that shuffling the same RR series, she or he can obtain a totally different statistical behaviour.

The main hypothesis on which research focused over the past decades is that HRV embed some physiological processes that are characteristics of regulatory systems acting on cardiovascular system.

Sympathovagal balance has been previously and extensively studied[2,3]. A transplanted heart shows a frequency higher than innervated heart. Injecting vagal blocking drugs (i.e. atropine) reproduce the same effect, increasing heart rate. On the other hand, blocking sympathetic nerves produce a slowing effect on heart rate. These two opposite effects brought to the concept of sympathovagal balance. Acting on one arm of the system, or on the other, not only affects heart rate per se, but also its variation in time and ultimately its distribution and statistical properties. Furthermore, sympathetic and vagal systems interact with each other, a phenomenon called *accentuated antagonism*[3]. This term relates to the observation that stimulus acting on the sympathetic side also causes a vagal response which partially attenuates the primary effect.

Although a simple relationship between sympathetic and vagal systems is appealing, research

showed a more complex behaviour. HRV dynamic is the result of multiple control systems acting on different scales of time, interacting with each other and also different in nature.

It is possible, though, to study such a complex system starting from RR intervals (which we will refer from now on with HRV) properties itself with the idea that any event affecting the cardiac regulatory system significantly will disrupt and change physiological HRV. This straightforward hypothesis is appealing and drove clinical research on HRV in several diseases such myocardial infarction (MI).

The first step is to derive a quantity able to represent and reproduce HRV behaviour. Such quantity needs to be reproducible and stable enough to allow comparison among patients and different conditions. Multiple algorithms have been created and applied, none of them showed superiority to the others and mostly, none have been proved to be the gold standard to be used in clinical practice.

In this article we review different methodologies previously published to calculate HRV indexes. We then searched literature for studies published on HRV and MI and we derive a metanalysis where published data allow calculation of composite outcomes.

Methods to Calculate HRV Indexes

We strongly encourage our readers to read references for single measures described below, since the purpose of this article is not to give a mathematical description and details but rather a conceptual view[4].

HRV can be analysed in time or frequency domain (Table I). Also, linear and non-linear methods exist.

Time Domain Indexes

It is the simplest way to calculate HRV. Time domain indexes include standard deviation of a series of all normal (i.e. sinus beats) RR intervals (SDNN), standard deviation of a mean RR intervals of a 5 minute ECG recording (SDANN), the square root of the average of the squares of the differences between consecutive RR intervals (RMSSD) and the percentage of RR intervals that differ each other more than 50 ms (pNN50). They are all correlated with each other, although RMSSD is preferred for its best statistics characteristics[5]. Important and complete review of the literature evidence that a less HRV measured with these methods show a worst prognosis or a higher mortality in patients with previous myocardial infarction, elderly and chronic heart failure[6-8].

Frequency Domain Indexes

Physiological data collected as a series in time, may be considered a sum of sinusoidal oscillations with distinct frequencies. Conversion from a time domain to frequency domain analysis is made possible with a mathematical transformation developed almost two centuries ago (1807) by the French mathematician Jean-Babtiste-Joseph Fourier (1768-1830). The amplitude of each sine and cosine wave determines its contribution to the biological signal; frequency domain analysis displays the contributions of each sine wave as a function of its frequency; the result of converting data from time series to frequency analysis is termed "spectral analysis" because it provides an evaluation of the power (amplitude) of the contributing frequencies to the underlying signal.

The heart rate spectrum analysis is used to evaluate the contribution on HRV of autonomic nervous system[7], a sensitive, quantitative and not invasive contribution in order to estimate the cardiovascular control system. SDNN is ultimately equal to the total power of spectral plot.

Normal HRV shows three dominant peaks: very low frequency (VLF) <0.04 Hz, affected by temperature regulation and it is abolished by atropine (parasympathetic efferent limb); low frequency (LF) between 0.04-0.15 Hz, considered related to sympathetic and parasympathetic activity; and high frequency (HF) between 0.15-0.4, synchronized to respiratory rhythm primarily related to vagal innervation.

Nonlinear (Fractal) Indexes

Power law exponent, Approximate Entropy (ApEn) and Detrended Fluctuation Analysis (DFA) are nonlinear methods recently introduced in HRV analysis.

If frequency domain indexes evaluate the contribution of single frequencies in a time series, power law exponent focuses on the nature of these correlations[8]. When equal to 1, it states that the time series has similar fluctuations acting at different scales, namely it is "scale invariant". In other words, patterns of variations are statistically similar regardless of the size of the variation. This scale invariant self-similar nature is a prop-

Table I. Time, Frequency and Nonlinear measures of HRV and their relationship.

Variability analysis	Time domain		Frequency domain	Nonlinear analysis		
Description	Statistical calculations of RR consecutive intervals	Frequency distribution	Spectral analysis	Power law	DFA	Entropy
Advantages/ Limitations	Easy to calculate/ Sensitive to artifact	Visual representation of data/Lacks widespread clinical application	Visual and quantitative representation of frequency contribution to waveform/Sensitive to artifact	Characterization of signal with single linear relationship; prognostication enabled/ large datasets required	Identify intrinsec variations VS external stimuli/Large datasets required	Fewest data required/ Needs Implementation
Output variables	SDNN, SDANN, RMSDD, pNN50	Skewness	Total power (area under the curve). VLF, LF, HF.	Slope/intercept of power law	Exponent $\alpha 1$, $\alpha 2$	ApEn

(From: Seely AJE, Macklem PA. Complex systems and the technology of variability analysis. Crit Care 2004; 8: R367-R384).
ApEn, approximate entropy; DFA, detrended fluctuation analysis; HF, high frequency; HRV, heart rate variability; LF, low frequency; RMSDD, root mean square of standard deviation; SD, standard deviation; DANN, standard deviation of 5 min averages; VLF, very low frequency.

erty of fractals, which are geometric structures pioneered and investigated by Mandelbrot[9].

DFA is also a technique that characterizes the pattern of variation across multiple scales of measurement. It is related to the power law exponent with a simple relation and thus has similar meaning. DFA was developed specifically to distinguish between intrinsic fluctuations generated by complex systems and those caused by external or environmental stimuli acting on the system[10]. Variations that arise because of extrinsic stimuli are presumed to cause a local effect, whereas variations due to the intrinsic dynamics of the system are presumed to exhibit long-range correlation.

Entropy is a measure of disorder or randomness, as embodied in the Second Law of Thermodynamics, namely the entropy of a system tends toward a maximum. Different states of a system tend to evolve from ordered configurations to configurations that are less ordered but statistically more probable. Related to time series analysis, ApEn provides a measure of the degree of irregularity or randomness within a series of data. ApEn was pioneered by Pincus[11] as a measure of system complexity; smaller values indicate greater regularity, and greater values convey more disorder, randomness and system complexity. As with other means of characterizing biological signals, ApEn has been most extensively studied in the evaluation of heart rate dynamics. Heart rate becomes more orderly with age and in men, showing decreased ApEn[12].

All these measures are considered "nonlinear" because they do not assume smoothness on the time series and are not affected by non-stationarity.

Literature Review and Metanalysis

Methods

Literature was searched using Pubmed® for articles on HRV and myocardial infarction. No restrictions on publication date were used. Articles were reviewed manually for pertinence and methodology and results were derived from original papers. No authors were contacted. Only original articles in English were considered. Each article's references list was reviewed for possible missing studies on previous search. Duplicate data were not considered. Where data were not available because not published and/or published in inadequate manner for subsequent metanalysis, the article was not further considered.

Articles considered eligible for metanalysis were original retrospective/prospective studies investigating HRV after MI, reporting follow up for mortality or significant cardiac complications. Primary end point for metanalysis was in fact total mortality.

Metanalysis was conducted according to previous published and accepted methodology, using the DerSimonian-Laird random effect[13]. Chi-square test was used to assess homogeneity among studies, setting a p value less than 0.10 as non-homogeneity indicator. Also Funnel plot was constructed to visually check for biases. After literature review (see below), SDNN was chosen for metanalysis parameter because of its broad use. We reviewed and considered studies where SDNN was reported as discrete value and cut-off reported by Authors (less or above 70 msec). Thus, results are shown as Odd Ratios of mortality/complications for single study and for the composite outcome. Where single numbers of deaths in the study group or control group was not reported, data were calculated using total numbers of patients enrolled and sensitivity, specificity, positive predictive value and negative predictive value. When this methodology led to some degree of approximation, generating non integer patient numbers in respective groups, we approximated data to nearest unit position.

Results

21 studies were identified as eligible for subsequent analysis. Among these studies 5 large trials were eligible for metanalysis (Table II). Three studies set SDNN cut-off at 50 msec, one at 65 msec and the remaining at 70 msec.

All patients were recorded for 24 hours using one lead standard Holter ECG after acute myocardial infarction. Time between MI and ECG recording ranged between 1 and 25 days. Follow up ranged between 14 and 1000 days. All studies used as primary end point mortality except for study from Pipilis et al[14] which considered as primary outcome all cardiac complications (mortality, heart failure, arrhythmia).

Therefore, metanalysis included 3489 total post-MI patients with an overall mortality of 125/577 (21,7%) in patients with SDNN less than 70 msec and 235/2912 (8,1%).

Funnel plot (Figure 2) did not visually showed significant biases. Test for homogeneity returned

Table II. Studies on HRV and MI.

Study	Year	No. of Patients	Δt REG. post-MI	ECG-recording duration	Analysis
Kleiger et al.[16]	1987	808	11 ± 3 gg	24 h	SD intervallo RR, RR medio
Cripps et al.[17]	1990	177	1-3 gg	24h	SD, triangular method
Pipilis et al.	1991	70	12,8 ± 6,6	24h	RR medio, SD RR medio, SD mean difference of each RR from previous RR
Farrell et al.[18]	1991	416	6-7 gg	24h	RR medio
Odemuyiwa et al.[19]	1991	385	5-10 gg	24h	Frequency distribution of RR interval duration
Bigger et al.[20]	1991	715	25 ± 17 gg	24h	Frequency domain: ULF, VLF, LF, HF, LF/HF ratio, total power
Bigger et al.[21]	1992	715	2 sett.	24h	Frequency domain: ULF, VLF, LF, HF, LF/HF ratio, total power
Bigger et al.[22]	1993	331	402 ± 21	24h	Frequency domain: ULF, VLF, LF, HF, LF/HF ratio, total power
Vaishnav et al.[23]	1994	226	48-180 h	24h	SDRR, SDANNi, SD, pNN50, RMSSD
Fei et al.[24]	1996	700	5-8 gg	24h	SDNN
Zuanetti et al.[25]	1996	567	NS	24h	SDNN, RMSSD, NN50
Copie et al.[26]	1996	579	5-11 gg	24h	RR medio
Bigger et al.[27]	1996	715	11 ± 3 gg	24h	Frequency domain: ULF, VLF, LF, HF, LF/HF ratio, total power
Quintana et al.[28]	1997	74	4 ± 2 gg	24h	NN medio, varianza, SDNN, SDANNi, RMSSD
Lanza et al.[29]	1998	239	5-20 gg	24h	Time domain: mean RR interval, mean SDANN, mean RR SD, RMSSD, pNN50; Frequency domain
La Rovere et al.[30]	1998	1284	6-28 gg	24h	SDNN
Huikuri et al.[31]	2000	446	5-10 gg	24h	Time domain, frequency domain, fractal measures, Poincarè plot, Power law scaling, detrended fluctuation
Tapanainen et al.[32]	2002	697	2-7 gg	24h	Time domain: mean RR interval, SDNN; spectral measures: ULF, VLF, LF, HF, LF/HF ratio; fractal measures: α_1, α_1 edited, α_2, α_2 edited, β
Carpeggiani et al.[33]	2003	413	0-48 h	24h	SDNN, SDNN index, SDANN, RMSSD, pNN50
Stein et al.[34]	2005	740	70 ± 121 gg	24h	Time domain, Frequency domain, nonlinear: power slope, SD12, DFA1
Dekker et al.35	2000	900	No CHD	2 min	SDNN, prognostic for CHD and Mortality

a Chi-Squared value of 6,38 corresponding to a p value of 0,17 with 4 degrees of freedom. Therefore, we were not able to reject the null hypothesis that a systematic bias exists among the five studies (i.e. there is homogeneity).

Figure 3 shows results using the Der Simonian-Laird method to combine single studies. The composite Odd Ratio for outcome (mortality) in two groups was 3,95 with 95% CI of 1,49-10,47.

Discussion

We focused on HRV and myocardial infarction. Even if multiple measures are available to quantify HRV dynamic, no gold standard has been defined yet. Furthermore, a single number magically able to discriminate between physiologic and pathologic states seems to be not realistic although appealing.

Despite that, HRV is simple to obtain, not expensive, non invasive and suitable for clinical practice.

SDNN and other indexes have been demonstrated to be an independent prognostic factor after acute MI. Patients at risk for mortality present lower SDNN. Metanalysis demonstrates that, after a MI, patients with SDNN below 70 msec on 24 hours ECG recording have almost 4 times more chance to die in the next 3 years. The composite Odd Ratio's CI was broad, but still did not

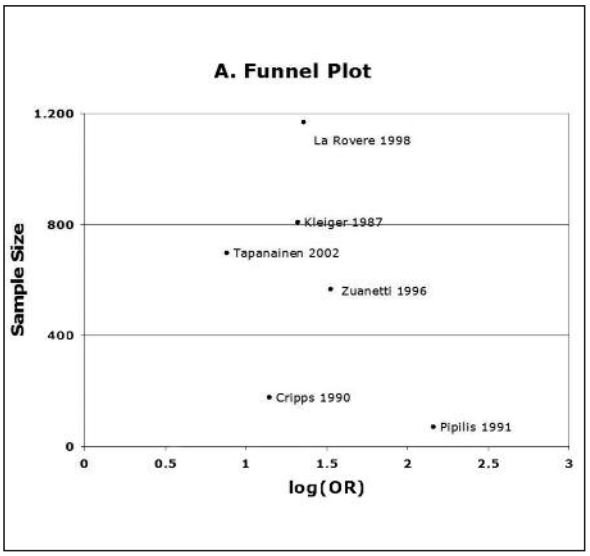

Figure 2. Funnel Plot.

include 1, indicating significant results. This "broadness" can be explained by several reasons. First, MI definition and classification changed over time. Second, HRV was recorded at different points in time (1 to 25 days). Third, different methods of ECG analysis (to derive RR intervals series) and different sampling rates were used by different Authors. Simply all these technical issues can affect the precision on which HRV is measured.

On a sub-analysis, although the overall homogeneity test did not reach significant level (p=0,17), most of the variability was due by the study of Pipilis et al. This is due to the fact that, in this paper, primary outcome was not only mortality but also other complications, such heart failure, and this particular study enrolled few patients compared to the others.

Results from other studies considered (but not included in the analysis) are consistent with the final finding, that a disrupted HRV dynamic is associated with higher adverse outcome.

SDNN is directly related to the total power calculated with Fourier analysis and it is correlated mostly to the vagal activity[15]. SDNN is obviously dependant on the total lengths of the series and it is affected by non-stationarity. In this perspective, although data are strongly positive for a direct relationship between SDNN and mortality after MI, SDNN value must be considered care-

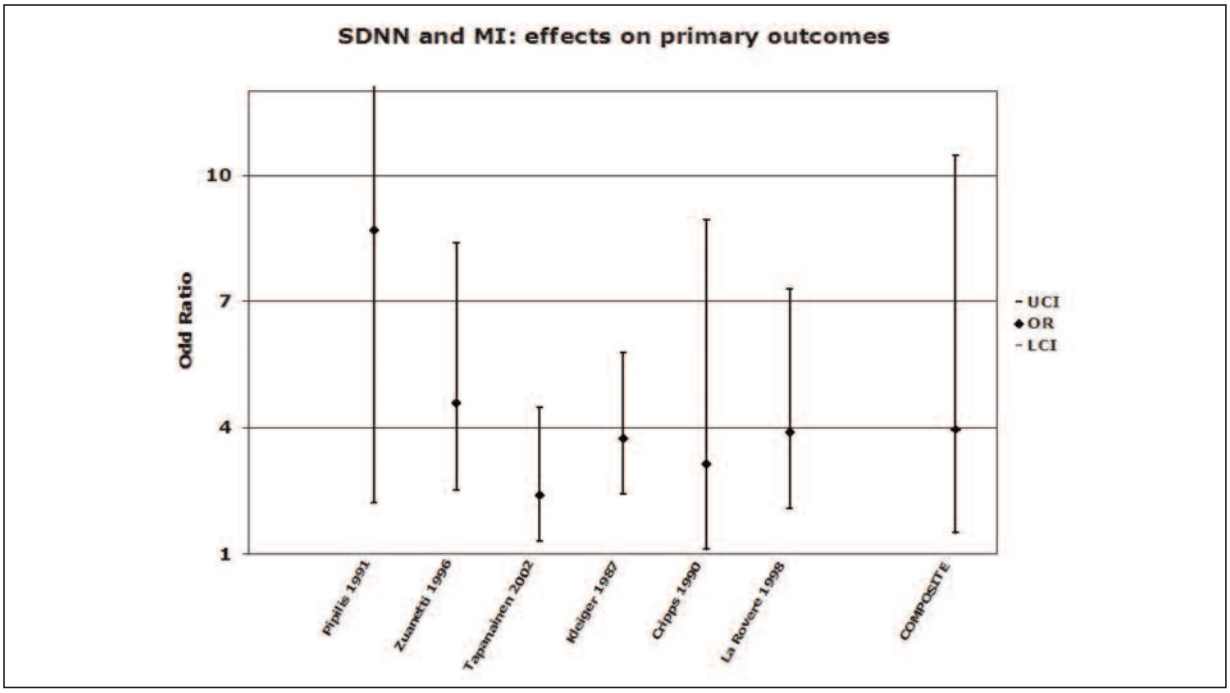

Figure 3. Metanalysis. Bars indicate OR and respective 95% CI for each study and for the opposite outcome. Study from Pilips 1991 has CI of 2.2-33.9. UCI is not shown for better overall scale adjustment. The overall Chi-squared was 6.38 with 4 degrees of freedom corresponding to p=0.17 indicating no significant non-homogeneity among studies. See text for other details and discussion.

fully on a single patient. The primary purpose of the metanalysis was to address whether studies conducted on HRV and MI were consistent rather than established a cut-off for SDNN.

Conclusions

Heart rate variability indicates the study of normal RR intervals series from chest surface ECG recording. RR intervals create a time series having linear and nonlinear properties, reflecting sympathovagal balance and cardiac tissue response to multiple stimuli and feedbacks.

Thus, HRV dynamic provides information about cardiovascular system regulation and is an independent prognostic factor in patient experienced a myocardial infarction. Post-MI patients who have SDNN less than 70 msec on 24-hours ECG recording, have 4 times more chance of mortality compare to those who have SDNN above 70 msec.

Other HRV measures demonstrated similar predictive properties although no gold standard, in terms of cut-off, has been demonstrated.

HRV is simple, non invasive and relatively not expensive to obtain. Further research is warranted to better understand and standardize the methodology.

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